UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **March 23, 2021**

SUBJECT: **Difenoconazole.** Human Health Risk Assessment for the Establishment of Tolerances with No U.S. Registrations in/on Japanese Persimmon, Olive, and Black Pepper.

PC Code: 128847
Decision Nos.: 555544, 557780, 562309
Petition Nos.: 9E8793 (Japanese Persimmon)
9E8814 (Olive)
0E8834 (Black Pepper)
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode Nos.: D455997, D457288, D458137
Registration No.: NA
Regulatory Action: Tolerance Petition

Case No.: 7014
CAS No.: 119446-68-3
40 CFR: §180.475

FROM: Bonnie Cropp-Kohlligian, Environmental Scientist
Minerva Mercado-Feliciano, Ph.D., DABT, Toxicologist
Thurston G. Morton, Senior Chemist
Carolyn Mottley, Biologist
Risk Assessment Branch IV
Health Effects Division (7509P)

THROUGH: Shalu Shelat, Branch Chief
Risk Assessment Branch IV
Health Effects Division (7509P)

TO: Kathryn Meyer, Risk Review Manager
Lindsay Roe, Product Manager 22
Cynthia Giles-Parker, Branch Chief
Fungicide Branch
Registration Division (RD; 7505P)

The Registration Division (RD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate the hazard data and conduct dietary (food and drinking water), residential, aggregate, and occupational exposure assessments to estimate the risks to human health that may result from the proposed new tolerances with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793), olive (Petition No. 9E8814), and black pepper (Petition No. 0E8834). The most recent comprehensive human health risk assessment for difenoconazole which was completed in 2020 for registration review (D457325, Cropp-Kohlligian, B. *et al*., 9/18/2020).-The prior toxicological endpoint selections are unchanged. Dietary and aggregate assessments were updated for this risk assessment. An updated residential exposure and risk assessment was not required. Since the proposed uses of difenoconazole are all non-domestic, no updates to the prior residential and non-occupational spray drift risk assessments are required and an occupational exposure and risk assessment is not required. No risks of concern were identified.

Table of Contents

1.0 Executive Summary

Difenoconazole is a broad-spectrum fungicide belonging to the triazole group of fungicides. It acts by blocking demethylation during sterol biosynthesis which, in turn, disrupts membrane synthesis. It is currently registered for use on a variety of crops in agricultural settings for foliar application, seed treatment, and post-harvest uses, and is also registered for use in residential settings on ornamentals and golf course turf. For agricultural uses, end-use products are formulated as suspension concentrates (SCs), flowable concentrates (FlCs), emulsifiable concentrates (ECs), ready-to-use solutions (RTUs), and emulsion [oil] in water solutions (EWs). For residential uses, end-use products are formulated as SCs, ECs, and RTUs. Additionally, for post-harvest uses, end-use products are formulated as FlCs and ECs. End use products have restricted entry intervals (REIs) ranging from 12 to 48 hours. As a seed treatment, it is applied with commercial grade or on-farm seed treatment equipment. As a foliar treatment, it is applied by commercial applicators using aerial, chemigation and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand-held sprayers.

Proposed Tolerances with No U.S. Registrations
Syngenta Crop Protection, LLC (hereafter referred to as Syngenta) is petitioning to establish tolerances with no U.S. registrations for residues of difenoconazole in/on Japanese persimmon imported from Japan (Petition No. 9E8793) and in/on olive imported from Greece (Petition No. 9E8814). American Spice Trade Association is petitioning to establish a tolerance with no U.S. registration for residues of difenoconazole in/on black pepper imported from Vietnam (Petition No. 0E8834).

Anticipated Exposure Pathways
For the proposed tolerances with no U.S. registrations. Since the proposed uses of difenoconazole are all non-domestic, the only potential exposure to residues of difenoconazole by humans from the proposed uses is from the consumption of imported Japanese persimmon, olive, and black pepper commodities that have been treated with difenoconazole.

For existing/registered uses. Humans may be exposed to difenoconazole in food and drinking water from the registered uses, since it may be applied directly to growing crops and application may result in difenoconazole reaching surface and ground water sources of drinking water. There are registered uses on commercial and residential landscapes and interior plantscapes, as well as turf applications to golf courses, that would result in residential handler and post-application exposures. The registered residential use sites for difenoconazole would not result in incidental oral exposure to children. However, potential non-occupational bystander exposure, which would include incidental oral exposure to children, may occur through spray drift from the existing uses. Occupational handlers may be exposed while mixing/loading the pesticide as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

Hazard Characterization
The toxicological database for difenoconazole is adequate for hazard characterization. Difenoconazole is rapidly absorbed and extensively distributed, metabolized, and excreted in rats. Blood levels of difenoconazole peaked at 2-4 hours in rats, and excretion half-life ranges

from 20 to 60 hours. Neither difenoconazole nor its metabolites bioaccumulate following oral exposure. The liver is the target organ in mice and rats; however, effects occur in mice at lower doses and with higher severity than in rats. After subchronic exposure, mice of both sexes showed hepatocellular hypertrophy and hepatic vacuolation, while females also showed coagulative necrosis. After chronic exposure, male mice showed individual cell necrosis and bile stasis, in addition to hepatocyte hypertrophy in both sexes. The liver effects in mice progressed from the subchronic to the chronic study, i.e. chronic effects occurred at lower doses than subchronic effects. Furthermore, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors (adenomas) in male and female mice. Apart from the liver effects in rodents, chronic exposure in dogs leads to lenticular cataracts. The acute eye irritation test in rabbits found mild irritation that was reversible in 4 days (Toxicity Category III). In dermal studies, no systemic toxicity was detected in rats or male rabbits, while in female rabbits, liver effects (minimal to moderate hepatocyte vacuolation and increased serum bilirubin levels) occurred at the limit dose (1000 mg/kg/day). Skin hyperkeratosis was detected in rats at the exposure site after repeated exposure to the limit dose. Slight skin irritation was detected after an acute single dose (Toxicity Category IV). Difenoconazole is not a skin sensitizer.

No quantitative susceptibility in fetus or offspring was seen in the database. A developmental study with difenoconazole in rats showed no significant fetal effects, while a developmental study in rabbits showed a slight increase in abortions (2/15 pregnant does). A guideline reproductive study in rats showed decreased pup weights and maternal body weight at the same doses but did not show any reproductive effects. Neurotoxicity was detected in an acute neurotoxicity battery study (decreased fore-limb strength in males only), but not in a subchronic neurotoxicity battery study with difenoconazole.

Dose Response Assessment

An uncertainty factor (UF) of 100X (10X to account for interspecies extrapolation and 10X for intraspecies variation) was applied to all points of departure (PODs) to obtain reference doses (RfDs). Since the Food Quality Protection Act Safety Factor (FQPA SF) has been reduced to 1X, population adjusted doses (PADs) are equivalent to their corresponding RfD. A margin of exposure (MOE) of 100 is the level of concern (LOC) for the short- and intermediate-term oral and inhalation exposure scenarios.

The acute POD for all populations is a no observed adverse effect level (NOAEL) of 25 mg/kg/day (aRfD of 0.25 mg/kg/day) based on reduced fore-limb grip strength in male rats on day 1 at the lowest observed adverse effect level (LOAEL) of 200 mg/kg/day. The chronic POD for all populations is a NOAEL of 4.7 mg/kg/day (cRfD of 0.05 mg/kg/day) based on increased incidence of liver lesions (individual cell necrosis and bile stasis in males, hepatocyte hypertrophy in both sexes), and increased serum levels of sorbate dehydrogenase in males at a LOAEL of 46 mg/kg/day in mice. The adult short-term oral, and short- and intermediate-term inhalation PODs are a NOAEL of 25 mg/kg/day based on increased incidence of late abortions at 75 mg/kg/day (LOAEL) in the developmental rabbit study. An incidental oral POD of 62 mg/kg/day was selected based on decreased body weight in females at 124 mg/kg/day in the 90-day rat study. This endpoint is appropriate for young children and protective of rat pup effects at 192 mg/kg/day (decreased body weight) in the reproductive study, and liver effects at 418 mg/kg/day in the 90-day mouse study. A dermal POD was not selected. The database does not

show systemic effects after exposure via the dermal route at doses that would be relevant to risk assessment. There is no concern for increased *in utero* or postnatal offspring susceptibility.

Dietary Exposure Assessment for Difenoconazole

Unrefined acute and partially refined chronic dietary exposure (food and drinking water) assessments were conducted for currently registered uses of difenoconazole and the pending tolerances with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793), olive (Petition No. 9E8814), and black pepper (Petition No. 0E8834). The unrefined acute assessment assumed tolerance-level residues, 100 percent crop treated (PCT), and the available empirical or HED's 2018 Default Processing Factors. The peak estimated drinking water concentration (EDWC) was used. The resulting acute exposure estimates were less than HED's level of concern (i.e., <100% of the aPAD) at the 95th percentile of the exposure distribution for the general U.S. population (17% aPAD) and all population subgroups. The most highly exposed population subgroup was all infants <1 year old at 53% of the aPAD. The partially refined chronic (food and drinking water) assessment assumed tolerance-level residues, the available empirical or HED's 2018 Default Processing Factors, and average percent crop treated (PCT) information for some commodities. The 1-in-10 year annual mean EDWC was used. The resulting chronic exposure estimates were less than HED's level of concern (i.e., <100% of the cPAD) for the general U.S. population (11% cPAD) and all population subgroups. The most highly exposed population subgroup was all infants <1 year old at 38% of the cPAD.

Quantification of cancer risk is not required. The RfD would address the concern for chronic toxicity, including carcinogenicity, likely to result from exposure to the pesticide.

Residential Exposure and Risk Assessment

An updated residential exposure and risk assessment was not required. Residential exposure and risk assessments were previously conducted for currently registered uses of difenoconazole under registration review (D457325, Cropp-Kohlligian, B. et al., 9/18/2020). There are no residential handler inhalation exposure and risk estimates of concern (i.e., MOEs are >LOC of 100). Inhalation exposures result in MOEs ranging from 3,200,000 to 340,000,000. A quantitative residential post-application assessment was not performed because a dermal endpoint was not selected. No residential use sites would result in incidental oral exposures in children (1 to < 2 years old).

Aggregate Risk Assessment

Aggregate exposure and risk assessments were conducted for currently registered uses of difenoconazole and the pending tolerances with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793), olive (Petition No. 9E8814), and black pepper (Petition No. 0E8834). Acute and chronic aggregate exposures to difenoconazole are anticipated to occur from food and drinking water uses only. Because no acute or chronic dietary risks of concern were identified, there are no risks of concern for acute and chronic aggregate exposures. Short-term aggregate risk was estimated by combining chronic dietary exposure (food + water) with the residential handler inhalation exposures from applications to gardens/ornamentals via hose-end sprayer. The resulting risk estimate is an MOE

of 5,000. There are no risks of concern from short-term aggregate exposure (i.e., MOEs are >LOC of 100). No intermediate-term aggregate exposure scenarios were identified.

Aggregate Assessment of Free Triazole & its Conjugates

Application of triazole-containing pesticides, such as difenoconazole, also result in exposure to free triazole and its conjugates, which are considered toxicologically different from difenoconazole and are assessed separately from the parent compound. The aggregate human health risk assessment for free triazole and its conjugates was updated for difenoconazole for registration review (D458929, Morton, T., 9/14/2020) and included the pending tolerances with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793), olive (Petition No. 9E8814), and black pepper (Petition No. 0E8834). The aggregate estimates remain below HED's level of concern.

Occupational Exposure and Risk Assessment

Since the proposed uses of difenoconazole are all non-domestic, there is no potential for domestic occupational exposures from the proposed uses. An occupational exposure and risk assessment is not required.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied (see Appendix C).

2.0 HED Conclusions

Pending submission of a revised section F of the olive petition (see Section 2.2.3. Revisions to Petitioned-For Tolerances), there are no issues that would preclude establishing the recommended tolerances with no U.S. registration for residues of difenoconazole in/on Olive; Olive, with pit; Pepper, black; and Persimmon, Japanese.

2.1 Data Deficiencies

There are no data deficiencies for the proposed tolerances with no U.S. registrations for residues of difenoconazole in/on imported olive (Petition No. 9E8814), black pepper (Petition No. 0E8834), and Japanese persimmon (Petition No. 9E8793).

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate tolerance enforcement method, gas chromatography with nitrogen-phosphorus detection (GC/NPD) method AG-575B, is available for the determination of residues of difenoconazole *per se* in/on plant commodities. An adequate enforcement method, gas chromatography with mass spectrometry detection (GC/MSD) method AG-676A, is also available for the determination of residues of difenoconazole *per se* in/on canola and barley commodities. A confirmatory method, GC/MSD method AG-676, is also available. The LOQs are 0.01-0.05 ppm.

An adequate tolerance enforcement method, Method REM 147.07b, is available for livestock commodities. The method determines residues of difenoconazole and CGA-205375 in livestock commodities by liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). The method LOQs are 0.01 ppm (for each analyte) for livestock tissues and 0.005 ppm (for each analyte) for milk. Adequate confirmatory methods, Method AG-544A and Method REM 147.06, are available for the determination of residues of difenoconazole and CGA-205375, respectively, in livestock commodities.

Adequate analytical reference standards for difenoconazole and CGA-205375 are currently available in the EPA National Pesticide Standards Repository (NPSR) and have expiration dates of 3/31/21 (email communication between T. Cole and B. Cropp-Kohlligian, 4/01/2019) and 4/30/21 (email communication between N. Mellor and B. Cropp-Kohlligian, 4/25/2019), respectively.

2.2.2 Recommended Tolerances

Tolerances are currently established under 40 CFR §180.475 and comply with the HED *Interim Guidance on Tolerance Expressions* (S. Knizner, 5/27/2009). Table 2.2.2.1 summarizes the recommended tolerance levels for Olive; Olive, with pit; and Persimmon, Japanese which were derived using the Organization for Economic Cooperation and Development Maximum Residue Level (OECD MRL) calculation procedure and the recommended tolerance level for Pepper, black which was derived using the spreadsheet for the procedures described by the Food and Agriculture Organization (FAO) of the United Nations Manual for establishing tolerance levels when using monitoring data (see 3rd Edition; FAO Plant Production and Protection Paper 225, Third Edition, ISSN 0259-2517; Section 5.11, page 103).

Table 2.2.2.1. Tolerance Summary for Difenoconazole (40 CFR §180.475)			
Commodity/ **Correct Commodity Definition**	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Under 40 CFR §180.475(a)(1)			
Olive[1]	--	3	Tolerance listing in 40 CFR Part 180 for pesticide residues in/on olives are currently listed as "Olive" and the commodity is defined in OCSPP Guideline 860.1000 as being the fruits after removal of the stems and pits, the commodity analyzed for enforcement.
Olive, with pit[1]	--	2	Commodity definition correction.[2]
Olive (including oil)	2	--	
Pepper, black[1]	0.1	0.1	
Persimmon, Japanese[1]	0.7	0.7	

1 Tolerance with no U.S. registration.

2 Chemistry Science Advisory Council (ChemSAC) meeting dates 4/10/2019 and 4/24/2019: ChemSAC recommended adding a commodity term of "Olive, with pit" for tolerance listings for the purposes of harmonization. For residue analysis, Codex also defines olive as the fruit after removal of the stem and pit; however, Codex stipulates that residues should be expressed on a whole-fruit basis.

2.2.3 Revisions to Petitioned-For Tolerances

Section F of the olive petition (Petition No. 9E8814) should be revised to correct commodity definitions as specified in Table 2.2.2.1 and include a proposed tolerance with no U.S. registration for residues of difenoconazole in/on Olive at 3 ppm. Tolerance listing in 40 CFR Part 180 for pesticide residues in/on olives are currently listed as "Olive" and the commodity is defined in OCSPP Guideline 860.1000 as being the fruit after removal of the stem and pit, the commodity analyzed for enforcement.

2.2.4 International Harmonization

Codex and Canada have established MRLs for residues of difenoconazole in/on olive commodities using the same data submitted in support of the U.S. tolerances with no U.S. registrations. Codex defines olive as the fruit after removal of the stem and pit; however, Codex stipulates that residues should be expressed on a whole-fruit basis. The U.S. recommended tolerance level for Olive, with pit (2 ppm) is harmonized with the Codex MRL for residues of difenoconazole in/on Table olives (2 ppm). Canada appears to have used the same data that Codex and the U.S. used but employed the NAFTA calculation procedure and established a tolerance in/on Olives at 2.5 ppm.

Codex and Canada have not established MRLs for residues of difenoconazole in/on Pepper, black. The default Canadian MRL for residues of difenoconazole in/on black pepper is 0.1 ppm.

A Codex MRL for difenoconazole has been established at 4 ppm in/on pome fruit for post-harvest use. Codex includes Japanese persimmon in the pome fruit group. The requested import use of difenoconazole on Japanese persimmon is a foliar use and; therefore, the tolerance cannot be harmonized with Codex. Canada has not established an MRL for residues of difenoconazole

in/on Japanese persimmon. Note: The default Canadian MRL for residues of difenoconazole in/on Japanese persimmon is 0.1 ppm.

Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes.

An International Residue Limit Status Sheet is attached in Appendix D.

2.3 Label Recommendations

None.

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of difenoconazole, its metabolites of concern for dietary risk assessment and/or the tolerance expression (i.e., CGA-205375 (found in livestock and drinking water) and OH-CGA-169374 (found in milk)), and the triazole metabolites are presented in Table 3.1.1.

Table 3.1.1. Difenoconazole Nomenclature.

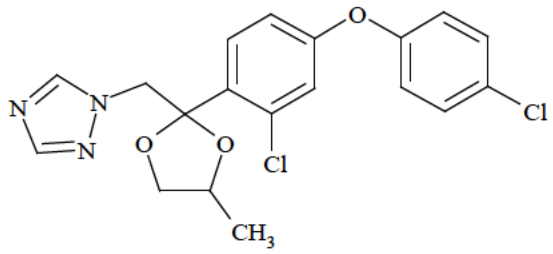
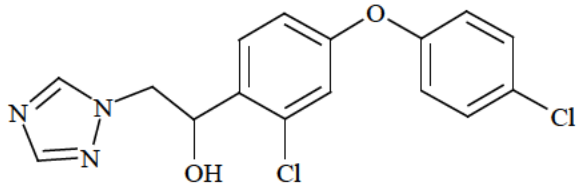
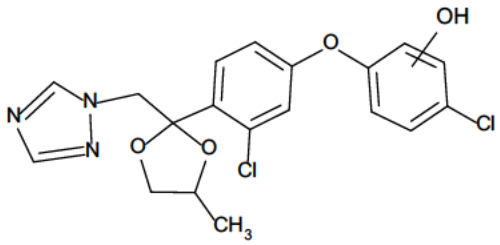
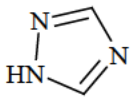
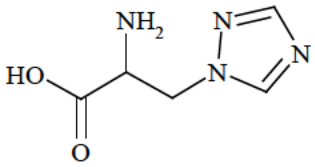
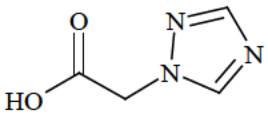
Chemical structure of parent	 mol. wt. 406.3
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-4-methyl-[1,3]dioxolan-2-ylmethyl]-1*H*-[1,2,4]triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]- 1*H*-1,2,4-triazole
CAS registry number	119446-68-3
Chemical structure of CGA-205375, livestock and drinking water metabolite	 mol. wt. 349.2

Table 3.1.1. Difenoconazole Nomenclature.	
Chemical structure of OH-CGA-169374 (hydroxy-difenoconazole), milk metabolite	
Chemical structure of 1,2,4-Triazole (1,2,4-T)	
Chemical structure of Triazolyl alanine (TA)	
Chemical structure of Triazolyl acetic acid (TAA)	

3.2 Physical/Chemical Characteristics

Difenoconazole possesses two chiral centers and it can exist in four stereoisomeric forms; however, the current analytical methods cannot distinguish between forms. Difenoconazole is a water soluble (3.3 ppm at 20 ºC) chemical. It has a relatively low vapor pressure (2.5×10^{-10} mm Hg at 25 ºC), which suggests that volatilization is not expected to be a major route of dissipation from soil and water. The octanol water partition coefficient (log Kow of 4.2 at 25 ºC) suggests that difenoconazole has a potential to bioaccumulate. More detailed physicochemical properties of difenoconazole are summarized in Appendix B.

3.3 Pesticide Use Pattern

Difenoconazole is a broad-spectrum fungicide belonging to the triazole group of fungicides. It acts by blocking demethylation during sterol biosynthesis which, in turn, disrupts membrane synthesis. It is currently registered for use on a variety of crops in agricultural settings for foliar application, seed treatment, and post-harvest uses, and is also registered for use in residential settings on ornamentals and golf course turf. For agricultural uses, end-use products are formulated as suspension concentrates (SCs), flowable concentrates (FlCs), emulsifiable concentrates (ECs), ready-to-use solutions (RTUs), and emulsion [oil] in water solutions (EWs). For residential uses, end-use products are formulated as SCs, ECs, and RTUs. Additionally, for post-harvest uses, end-use products are formulated as FlCs and ECs. End use products have REIs ranging from 12 to 48 hours. As a seed treatment, it is applied with commercial grade or on-farm seed treatment equipment. As a foliar treatment, it is applied by commercial applicators using

aerial, chemigation and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand-held sprayers.

All registered labels require occupational handlers to wear baseline attire (long-sleeved shirt, long pants, shoes, and socks). Some labels require PPE, in the form of gloves, coveralls, and in some cases, a NIOSH-approved respirator. In some cases, registered labels do not include requirements for PPE or clothing for residential handlers.

Use Directions for Olive. Under section B of petition 9E8814, Syngenta submitted proposed directions for use of difenoconazole in Greece on olives for import into the U.S. Difenoconazole, formulated as an EC at 25% w/v (250 g ai/L end-use product named Score 25EC), is used in Greece on olives. The maximum use rate is two foliar applications at 500 ml of product/ha (i.e., 0.125 kg ai/ha/application and 0.250 kg ai/ha/season). The retreatment interval (RTI) is 14-days. The preharvest interval (PHI) is 30-days. Application is made when fruit size is about 50% of final size (BBCH 75-85). The proposed use directions are adequate to allow evaluation of the residue data relative to the proposed uses of difenoconazole.

Use Directions for Black Pepper. Under section B of petition number 0E8834, the American Spice Trade Association submitted proposed directions for use of difenoconazole in Vietnam on black pepper for import into the U.S. Use directions taken *verbatim* from the petition are provided below in Table 3.3.1 and are considered adequate.

Table 3.3.1. Use Directions for Difenoconazole Products Registered in Vietnam for Use on Pepper, Black.

Product Active Ingredients	Dosage	PHI[1]
Difenoconazole 125 g/l + Azoxystrobin 200 g/l	400-500 liter/hectare	10 days
Difenoconazole 150 g/l + Azoxystrobin 200 g/l	400 liter/hectare	15 days
Difenoconazole 150 g/l + Azoxystrobin 250 g/l	275-300 liter/hectare	7 days
Difenoconazole 200 g/kg + Azoxystrobin 60g/kg + Dimethomorph 100 g/kg	350-400 g/hectare	7 days

1 PHI = pre-harvest interval.

Use Directions for Japanese Persimmon. Under section B of petition 9E8793, Syngenta submitted proposed directions for use of difenoconazole in Japan on Japanese persimmon for import into the U.S. Difenoconazole, formulated as a water dispersible granule (WDG) at 10% w/w (product name Score WG (A8885J)), is used in Japan on Japanese persimmon. The maximum use rate is three late season foliar applications up to 700 L/10a with a 3000x dilution factor, which corresponds to 233 g ai/ha. No RTI is specified. The PHI is 1-day.

3.4 Anticipated Exposure Pathways

Since the proposed uses of difenoconazole are all non-domestic, the only potential exposure to residues of difenoconazole by humans from the proposed uses is from the consumption of imported Japanese persimmon, olive, and black pepper commodities that have been treated with difenoconazole. From the registered domestic uses of difenoconazole, humans may be exposed

to difenoconazole in food and drinking water, since it may be applied directly to growing crops, and application may result in difenoconazole reaching surface and ground water sources of drinking water. There are registered uses on commercial and residential landscapes and interior plantscapes, as well as turf applications to golf courses, that would result in residential handler and post-application exposures. The registered residential use sites for difenoconazole would not result in incidental oral exposure to children. However, potential non-occupational bystander exposure, which would include incidental oral exposure to children, may occur through spray drift from the existing uses. Occupational handlers may be exposed while mixing/loading the pesticide as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

The hazard characterization and dose-response assessment for difenoconazole was updated for the registration review of difenoconazole (D457325, Cropp-Kohlligian, B. *et al.*, 9/18/2020) and is restated herein. There have been no changes since registration review.

4.1 Toxicology Studies Available for Analysis

The toxicological database for difenoconazole is adequate for hazard characterization. All toxicity studies required in accordance with 40 CFR Part 158 have been submitted, except for an

inhalation toxicity study which is not recommended to be required at this time (TXR 0054074, Smegal, D., 3/05/2012).

The available toxicological studies with difenoconazole that are usable for risk assessment are summarized in Appendix A.1 and A.2, and include the following:

- A battery of acute toxicity studies
- Subchronic oral toxicity studies in rat and mouse,
- Subchronic dermal toxicity studies in rabbit and rat,
- Prenatal developmental studies in rat and rabbit,
- Reproduction and fertility effects study in rat,
- Chronic toxicity studies in dog,
- Carcinogenicity study in mouse,
- Combined chronic/carcinogenicity study in rat,
- A battery of genetic toxicity studies,
- Acute and subchronic oral neurotoxicity studies,
- Metabolism and pharmacokinetic study,
- Dermal penetration studies, and
- Immunotoxicity study.

A broad survey of the literature was conducted to identify studies that report toxicity following exposure to difenoconazole via exposure routes relevant to human health pesticide risk assessment not accounted for in the agency's difenoconazole toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 24 studies from the literature. During title/abstract and/or full text screening of these studies, 1 was identified as containing potentially relevant information (either quantitative or qualitative) for the difenoconazole human health risk assessment. Following a full text review of the identified relevant study, it was determined that this study does not contain information that would impact the risk assessment and was not considered in the selection of endpoints or PODs. Appendix A.3 has detailed information regarding the literature review.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in rats after administration of a single low and/or high dose (0.5 or 300 mg/kg, respectively) or repeated low dose (0.5 mg/kg). The test compound was labeled with C^{14} at either the phenyl or triazole ring. Difenoconazole was rapidly absorbed and extensively distributed, metabolized, and excreted in rats, regardless of dosing regimens. Distribution and metabolism of difenoconazole were similar in both sexes. Biliary excretion was the main route of elimination with some dose and sex dependency (75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In bile duct cannulated rats, more of the administered dose (AD) was eliminated in the urine or bile at 0.5 mg/kg (9-14% and 73-75%, respectively) versus 300 mg/kg (1% and 39-56% respectively), and more of the AD was eliminated in feces (2-4% at 0.5 mg/kg vs. 17-22% at 300 mg/kg,

respectively), indicating saturation of absorption. Half-lives of elimination are approximately 20 hours for the low dose and 33-48 hours for the high dose. Radioactivity in the blood peaked at 2 to 4 hours at the low and high dose, respectively.

Difenoconazole undergoes successive oxidation and conjugation reactions. Following administration of 300 mg/kg of phenyl-labeled difenoconazole, three major urinary metabolites were identified as isomers of OH-CGA 205375 (6% of dose), sulfate conjugates (and their isomers) of OH-CGA 205375 (3.9% of dose), and the hydroxyacetic metabolite of OH-CGA 205375 (2.0% of dose). No single unknown urinary metabolite accounted for >1.1% of the dose. Free triazole metabolite was detected in the urine of the triazole-label groups, and its byproduct was detected in the liver of phenyl-labeled groups only.

The study results indicate that difenoconazole and/or its metabolites do not bioaccumulate appreciably following oral exposure since all tissues contained negligible levels (<1%) of radioactivity 7-days post exposure.

4.2.1 Dermal Absorption

In vivo dermal absorption studies in the rat and *in vitro* dermal absorption studies in rat and human skin are available for difenoconazole (Appendix Table A.2.3) and were previously reviewed in detail (TXR 0056473, Chen, J., 12/18/2008). An estimated *in vivo* dermal absorption of 48% in rats exposed for 6 hours was determined by combining the remaining dose at the skin exposure site (including tape strips) with total excretion and dose remaining in the carcass at 24 hours after exposure at the lowest dose tested (0.5 $\mu g/cm^2$). An estimated human/rat *in vitro* absorption ratio of 0.12 was the highest calculated ratio from a 24-hour exposure assay. The resulting dermal absorption factor (DAF) of 6% (*in vivo* rat × *in vitro* rat-to-human ratio = 48% × 0.12 = 5.76%) is a refined estimate of dermal absorption in humans.

4.3 Toxicological Effects

The difenoconazole toxicology database underwent extensive review for registration review, and most studies have been updated to reflect current toxicology evaluation practices. The liver is the target organ in mice and rats; however, liver effects occur in mice at lower doses and with higher severity than in rats. After subchronic exposure, both rats and mice showed hepatocellular hypertrophy at similar doses; however, mice also showed minimal to moderate hepatic vacuolation in both sexes and coagulative necrosis in females. After chronic exposure, rats continued to show only adaptive liver effects (hepatocyte hypertrophy and pigmented macrophages). However, at similar doses as those leading to rat adaptive effects, mice showed individual cell necrosis and bile stasis in males, in addition to hepatocyte hypertrophy in both sexes. The liver effects in mice progressed from the subchronic to the chronic study, i.e. in the chronic study effects occurred at lower doses than in the subchronic study, and together with hepatocellular adenoma and carcinoma in males and adenomas in females. Apart from the liver effects seen in rodents, the target organ in dogs is the eye lens. Chronic exposure in dogs leads to lenticular cataracts. The acute eye irritation test in rabbits found mild irritation that was reversible in 4 days (Toxicity Category III).

In dermal studies, no systemic toxicity was detected in rats, while in rabbits, liver effects (minimal to moderate hepatocyte vacuolation and increased serum bilirubin levels) were observed in females only at the limit dose (1000 mg/kg/day). Skin hyperkeratosis was detected in rats at the exposure site after repeated exposure to the limit dose. Slight skin irritation was detected after an acute single dose (Toxicity Category IV). Difenoconazole is not a skin sensitizer.

No quantitative susceptibility in fetuses or offspring was seen in the database. A developmental study with difenoconazole in rats showed no significant fetal effects, while a developmental study in rabbits showed a slight increase in abortions (2/15 pregnant does) on gestation days 18 and 24. A guideline reproductive study in Sprague-Dawley rats showed decreased pup weights at the same doses as maternal effects (decreased body weight) but did not show any reproductive effects. In a study from the published literature (Ribas Pereira *et al.* 2019) the sperm in Wistar rats gavaged for 30 days showed decreased motility, a decrease in percentage with normal morphology, decreased acrosomal integrity, and decreased number of spermatozoa. However, that study tested a formulation of difenoconazole (the toxicity of the inert components is not known), and the results have not been corroborated by other studies. Sperm parameters were not measured in the guideline study with Sprague-Dawley rats.

Neurotoxicity was detected in an acute neurotoxicity battery study (decreased fore-limb strength in males only), but not in a subchronic neurotoxicity battery study with difenoconazole. There is no other indication of neurotoxicity in the difenoconazole database.

In an immunotoxicity study in mice, decreased mean immunoglobin M levels were detected at dose levels ≥ 177 mg/kg/day. There is no other indication of immunotoxicity in the difenoconazole database.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[2]

The FQPA SF for infants and children may be reduced to 1X. The difenoconazole database is sufficient for a full hazard evaluation. The only study that showed neurotoxicity is used as point of departure for risk assessment and the effect is well characterized with a clear NOAEL and LOAEL. There is no increased susceptibility to fetuses or offspring. There are no residual uncertainties in the exposure database.

4.4.1 Completeness of the Toxicology Database

The toxicity database is sufficient for a full hazard evaluation and to evaluate risks to infants and children, as well as neurotoxicity. The following studies were used in this evaluation: prenatal developmental studies in rat and rabbit; reproduction and fertility effects study in rat; and acute and subchronic oral neurotoxicity studies. An inhalation toxicity study is not recommended to be required at this time (TXR 0054074, Smegal, D., 3/05/2012).

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.4.2 Evidence of Neurotoxicity

There are signs of neurotoxicity in the acute neurotoxicity battery study (decreased fore-limb strength in males), but not in the subchronic neurotoxicity battery study, nor in any other studies in the database. This risk assessment is protective of the observed neurotoxicity effects because they are used to establish the point of departure (POD) for the acute oral assessment.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The available toxicity studies indicated no increased offspring susceptibility in rats or rabbits from *in utero* or postnatal exposure to difenoconazole. No fetal effects were detected in rats. Fetal effects in rabbits and pup effects in rats occurred at the same doses as maternal effects.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative (i.e., both the acute and chronic assessments used tolerance-level residues and, while the acute assessment assumed 100% crop treated, the chronic assessment used average percent crop treated data for some commodities) and will not underestimate dietary exposure to difenoconazole. The residential exposure assessments for the existing uses are based upon the 2012 Residential Standard Operating Procedures (SOPs) and incorporate chemical-specific turf transferable residue (TTR) data. These assessments of exposure are not likely to underestimate the resulting risk estimates from exposure to difenoconazole.

4.5 Toxicity Endpoint and Point of Departure Selections

Toxicity endpoints and PODs for dietary (food and water), occupational, and residential exposure scenarios are summarized below. Points of departure have been revised as part of registration review and the updates were included in the most recent risk assessment conducted for registration review (D457325, Cropp-Kohlligian, B. *et al*., 9/18/2020). A detailed description of the studies used as a basis for the selected endpoints is presented in Appendix A.

An acute POD of 25 mg/kg/day (no observed adverse effect level; NOAEL) was selected from an acute neurotoxicity study in rats based on reduced fore-limb grip strength in males on day 1 at the lowest observed adverse effect level (LOAEL) of 200 mg/kg/day. An uncertainty factor (UF) of 100X (10X to account for interspecies extrapolation and 10X for intraspecies variation) was applied to the NOAEL to obtain an acute reference dose (aRfD) of 0.25 mg/kg/day. Since the FQPA factor has been reduced to 1X, the acute population adjusted dose (aPAD) is equivalent to the aRfD. The selected endpoint is appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations with acute exposures.

A chronic POD of 4.7 mg/kg/day (NOAEL) was selected from a chronic/carcinogenicity oral study in mice based on increased incidence of liver lesions (individual cell necrosis and bile stasis in males, hepatocyte hypertrophy in both sexes), and increased serum levels of sorbitol dehydrogenase in males at a LOAEL of 46 mg/kg/day. A UF of 100X (10X to account for

interspecies extrapolation and 10X for intraspecies variation) was applied to the (rounded) dose to obtain a chronic reference dose (cRfD) of 0.05 mg/kg/day. Since the FQPA factor has been reduced to 1X, the chronic population adjusted dose (cPAD) is equivalent to the cRfD.

Adult short-term oral, and short- and intermediate-term inhalation PODs of 25 mg/kg/day (NOAEL) were selected from a rabbit developmental toxicity study based on increased incidence of late abortions at 75 mg/kg/day (LOAEL). There is no route-specific study for inhalation exposure, and so inhalation is assumed to be equivalent to oral exposure. This endpoint is protective of all other adult effects in the difenoconazole database. A margin of exposure (MOE) of 100 is the level of concern (LOC) for the short- and intermediate-term oral and inhalation exposure scenarios based on the conventional uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variation).

An incidental oral POD of 62 mg/kg/day (NOAEL) was selected based on decreased body weight in females at 124 mg/kg/day (LOAEL) in the 90-day rat study. This endpoint is appropriate for young children and protective of rat pup effects at 192 mg/kg/day (decreased body weight) in the reproductive study, and liver effects at 418 mg/kg/day in the 90-day mouse study. The LOAEL (on which this POD is based) is numerically lower than the LOAEL on which the acute dietary POD is based due to the dose spacing in each of the studies. Nevertheless, the POD (i.e. the NOAEL) for the acute endpoint is lower than the POD for the incidental oral endpoint. In addition, the selected endpoint is appropriate for incidental oral exposure because effects were seen after several doses. An MOE of 100 is the LOC for the incidental oral exposure scenarios based on the conventional uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variation).

A dermal POD was not selected. The database does not show systemic effects after exposure via the dermal route at doses that would be relevant to risk assessment. A route-specific study in rabbits showed liver effects of minimal to moderate severity at the limit dose (1000 mg/kg/day), which are considered an inflection point in the dose-response curve. Applying the 6% DAF to oral short- and intermediate-term studies in the database yields LOAELs above the limit dose, which are not relevant to risk assessment. There is no concern for increased *in utero* or postnatal offspring susceptibility.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential residential exposures to a pesticide, the risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Toxicological effect for the dietary oral (liver) and incidental oral for children (body weight) routes are different, therefore, these routes cannot be combined. The toxicological effect for adult oral and inhalation routes is the same (late abortions), therefore, these routes of exposure can be combined.

4.5.2 Cancer Classification and Risk Assessment Recommendation

In accordance with EPA's 2005 Guidelines for Carcinogenic Risk Assessment, difenoconazole was re-classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors in male and female mice (TXR 0054532, D318039, Shah, P., 3/01/2007). Difenoconazole is not genotoxic, and there is no evidence of carcinogenicity in rats. Quantification of cancer risk is not

required. The RfD would address the concern for chronic toxicity, including carcinogenicity, likely to result from exposure to the pesticide.

4.5.3 Summary of Points of Departure and Toxicity Endpoints

Table 4.5.3.1. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = aPAD = 0.25 mg/kg/day	Acute neurotoxicity in rats (MRID 46950327) LOAEL = 200 mg/kg based on decreased fore-limb strength at the time of peak effect in males.
Chronic Dietary (All Populations)	NOAEL = 4.7 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = cPAD = 0.05 mg/kg/day	Carcinogenicity in mouse (MRID 42090015) LOAEL = 46 mg/kg/day based on increased incidence of liver lesions (individual cell necrosis and bile stasis in males, hepatocyte hypertrophy in both sexes), and increased serum levels of SDH in males.
Incidental Oral Short-Term (1-30 days)	NOAEL = 62 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	90-Day oral toxicity in rat (MRID 42090022) LOAEL = 124 mg/kg/day based on decreased body weights in females (≥10%).
Adult Oral Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	Prenatal developmental toxicity in rabbit (MRID 42090017) Maternal/fetal LOAEL = 75 mg/kg/day based on abortions (2/15 pregnant) on gestation days 18 and 24.
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	Prenatal developmental toxicity in rabbit (MRID 42090017) Maternal/fetal LOAEL = 75 mg/kg/day based on abortions (2/15 pregnant) on gestation days 18 and 24.
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	The database does not show systemic effects after exposure via the dermal route at doses that would be relevant to risk assessment, and there is no concern for increased *in utero* or postnatal offspring susceptibility.			
Cancer (oral, dermal, inhalation)	Classification: Suggestive Evidence of Carcinogenic Potential. Quantification of cancer risk is not required. The RfD would address the concern for chronic toxicity, including carcinogenicity, likely to result from exposure to the pesticide.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-

observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4.5.3.2. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	The database does not show systemic effects after exposure via the dermal route at doses that would be relevant to risk assessment, and there is no concern for increased *in utero* or postnatal offspring susceptibility.			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	Prenatal developmental toxicity in rabbit (MRID 42090017) Maternal/fetal LOAEL = 75 mg/kg/day based on abortions (2/15 pregnant) on gestation days 18 and 24.
Cancer (oral, dermal, inhalation)	Classification: Suggestive Evidence of Carcinogenic Potential. Quantification of cancer risk is not required. The RfD would address the concern for chronic toxicity, including carcinogenicity, likely to result from exposure to the pesticide.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). MOE = margin of exposure. LOC = level of concern.

Note: Since the inhalation POD is based on maternal and fetal effects, the adult body weight appropriate for inhalation assessments is 69 kg. For children 1 to < 2 years old, the body weight appropriate for incidental oral assessments is 11 kg.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue in plants is understood based on acceptable plant metabolism studies reflecting foliar applications in canola, grape, potato, tomato, and wheat, and seed treatment in wheat. The residue of concern for both tolerance enforcement and risk assessment for crops included in this petition is difenoconazole only. The nature of the residue in livestock is understood based on acceptable goat and hen metabolism studies. The residues of concern for both tolerance enforcement and risk assessment for livestock commodities are difenoconazole and its metabolite CGA-205375. In addition, metabolite OH-CGA-169374, which comprised 15% of the total radioactive residue (TRR) in goat milk from the phenyl-labeled study, should be considered as a residue of concern in milk for the dietary risk assessment.

The nature of the residue in rotational crops is adequately understood. The metabolism of difenoconazole in rotational crops is similar to that of primary crops. The available

difenoconazole confined and limited field rotational crop trials are deemed adequate to satisfy data requirements under Guidelines 860.1850 and 860.1900. Taken together, these data support a 30-day plantback interval (PBI) for cereal and root/tuber crops not already registered for foliar use with difenoconazole and a 60-day PBI for all other crops not already registered for foliar use with difenoconazole. With these PBIs, tolerances for residues of difenoconazole are not needed for rotational crops.

5.1.2 Summary of Environmental Degradation

Difenoconazole has the potential to reach surface water via run-off, erosion, and spray drift, and is less likely to reach ground water except in soils of high sand and low organic matter content. Environmental fate data indicate that difenoconazole is relatively stable to aerobic and anaerobic soil metabolism and aerobic and anaerobic aquatic metabolism. When applied at 0.1-0.23 ppm to an aerobic soil, difenoconazole appears to degrade with half-lives ranging from 84.5 to 533 days based on laboratory studies conducted on a variety of foreign and domestic soils. At concentrations of 10 ppm, difenoconazole degraded with the half-lives of 1059-1600 days in aerobic, and 947 days anaerobic loam soil, respectively. In aquatic environments under aerobic conditions, difenoconazole microbially degraded with half-lives ranging from 315 to 565 days at concentrations up to 0.17 mg ai/L, and 860 days in a concentration of 10 mg ai/L. Under anaerobic conditions, difenoconazole degraded in 370 days at a concentration of 0.04 mg ai/L, and 1245 days at a concentration of 10 mg ai/L. The longer half-life values obtained for those higher concentration rates implies that the rate of difenoconazole microbially- mediated degradation may be concentration dependent. In laboratory studies on difenoconazole, a significant amount of radioactivity was nonextractable (14.4 to 48.9%) from soils.

Considering abiotic degradation, difenoconazole is photolyzed in water (half-life of 6 to 228 days), but stable in soil. The half-life of 228 days was extrapolated from a 15-day study in which difenoconazole slowly photolyzed from 100% to 91% under artificial light conditions (MRID 46950105). Also, the compound is stable to hydrolysis at pH values from 4 to 9.

Difenoconazole degraded with half-lives ranging from 139 to 462 days in terrestrial field dissipation studies. The overall stability of the compound in the terrestrial environment suggests that difenoconazole may accumulate in soil with successive applications from year to year.

5.1.3 Comparison of Metabolic Pathways

Little information is available on the toxicity of the major difenoconazole metabolites. The CGA-205375 metabolite formed in livestock appears to be formed in the rat also and is, therefore, part of the total toxic exposure for these animals.

5.1.4 Residues of Concern Summary and Rationale

Residues of concern were determined based on recommendations from the HED Residues of Concern Knowledgebase Sub-committee (ROCKS; Irwin, W., 9/19/2011, D391350). The residue of concern for plant commodities for tolerance enforcement and risk assessment purposes is difenoconazole only. The parent compound and the CGA-205375 metabolite are the residues of

concern in livestock commodities for both the tolerance enforcement and the risk assessment. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern in milk for the dietary risk assessment. Based on available goat metabolism data, total residues of concern in milk for dietary risk assessments (parent, CGA-205375 and OH-CGA-169374), should be calculated by multiplying the tolerance in milk by a factor of 1.5x. For drinking water, the parent compound and the CGA-205375 metabolite should be considered in the risk assessment.

Table 5.1.4.1 summarizes tolerance expression and the residues of concern in plant and livestock commodities.

Difenoconazole belongs to the triazole group of fungicides. The triazole metabolites common to the group, 1,2,4-triazole (1,2,4-T), triazolylalanine (TA) and triazolylacetic acid (TAA), are residues of concern for risk assessment purposes and are assessed separately from the parent compound.

Table 5.1.4.1. Difenoconazole Residues of Concern in Plants and Ruminants.

Matrix		Residues of Concern	
		For Risk Assessment	For Tolerance Expression
Plants	Primary and Rotational crops	Parent Only	Parent Only
Livestock	Ruminant and Poultry	Parent and CGA 205375	Parent and CGA 205375
	Milk	Parent, CGA 205375 and OH-CGA-169374	Parent and CGA 205375
Drinking Water		Parent and CGA 205375	NA

Note: The triazole-containing metabolites 1,2,4-T, TA, and TAA should be included in the residues of concern for risk assessment purposes only for plant and livestock commodities. Since these metabolites are common to the entire class of triazole-containing fungicides and because of differential toxicity between metabolites and the various parent compounds, risks associated with exposure to 1,2,4-T and to TA/TAA are addressed separately.

5.2 Food Residue Profile

Difenoconazole is registered on a wide range of agricultural crops and may be applied as a foliar treatment and/or as a seed-treatment and/or as a post-harvest treatment. Difenoconazole is generally slowly absorbed and metabolized in plants. Residues are most likely to be surface residues from direct applications or from post-harvest applications, and quantifiable residues in harvested crops are likely. The parts of the plant not directly exposed are more likely to contain a residue dominated by the mobile water-soluble triazole metabolites. Difenoconazole appears relatively stable and has a tendency to concentrate in oils and dried processed commodities. Difenoconazole residues are reasonably persistent in soils. The confined rotational crop studies demonstrate that difenoconazole itself does not appear as a residue in the rotational crop. The mobile water-soluble triazole metabolites have been identified in the rotational crops. In animals, difenoconazole is rapidly metabolized, initially to CGA 205375 and then with cleavage of the triazole moiety from the chlorophenoxyphenyl moiety. Residues are higher in the liver than in other tissues.

For Olive (Petition Number 9E8814; D457342, Cropp-Kohlligian, B., 3/23/2021). Syngenta submitted olive field trial data reflecting the maximum proposed use rate for difenoconazole on

olives. These data are adequate to support a tolerance with no U.S. registration for residues of difenoconazole in/on olive. Tolerance listings in 40 CFR Part 180 for pesticide residues in/on olives are currently listed as "Olive", and the commodity is defined in OCSPP Guideline 860.1000 as being the fruits after removal of the stems and pits, the commodity analyzed for enforcement. However, Chemistry Science Advisory Council (ChemSAC) recommended adding a commodity term of "Olive, with pit" for tolerance listings for the purposes of harmonization (meeting dates 4/10/2019 and 4/24/2019). Hence, two tolerance listings are being recommended for olive: Olive and Olive, with pit. Using OECD MRL calculation procedures, the recommended tolerances in/on Olive and Olive, with pit are 3 ppm and 2 ppm, respectively.

Syngenta also submitted olive processing data for difenoconazole. Residues of difenoconazole concentrate in oil processed from whole fruit (fruit w/pit) by as much as 1.5x. [Note: This estimated concentration would be lower if based on olive without pit. Processing factors based on comparison with the olive without pit cannot be calculated since the weight of the pits was not provided in the submission.] Based on the highest average field trial (HAFT) for whole fruit (fruit w/pit), which was 1.15 ppm, and the average concentration factor for oil (1.5x), the maximum residue in oil is estimated at 1.7 ppm and below the proposed/recommended tolerance for residues of difenoconazole in/on Olive, with pit (2 ppm). Therefore, a separate tolerance for residues of difenoconazole in Olive, oil is unnecessary at this time.

For Black Pepper (Petition Number 0E8834; D458676, Cropp-Kohlligian, B., 3/23/2021). ChemSAC (see ChemSAC minutes from 5/10/2017 and subsequent amendment (dated 11/30/2018) to the proposed solution) has recommended that monitoring data can be used *in lieu* of field trial data for establishing import tolerances for residues of pesticides in/on imported spices using procedures described by the FAO to establish the tolerance level. The procedures are described in the FAO Manual for the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed (3rd Edition; FAO Plant Production and Protection Paper 225, Third Edition, ISSN 0259-2517; Section 5.11, page 103), and a tolerance spreadsheet for determining the specified percentile and non-parametric upper confidence limit for a set of numbers is used for calculating the recommended tolerance.

According to the petitioner, the American Spice Trade Association, difenoconazole is approved for use on black pepper in Vietnam, and the majority of black pepper imported into the U.S. comes from Vietnam. *In lieu* of field trial data, the petitioner has submitted monitoring data for residues of difenoconazole in/on black pepper collected using a QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) multiresidue method. The data consist of a total of 1,920 samples of black pepper collected from a number of countries during 2009-2015, 2017, and 2018. Of the 1,920 samples tested, 404 samples (21% of samples tested) had quantifiable residues of difenoconazole with levels ranging from 0.005-1.2 ppm, and 1,516 samples were reported as having 0 ppm. Most of the monitoring data are for black pepper originating from Vietnam (i.e., 1,415 of the 1,920 samples tested and 347 of the 404 samples with quantifiable residue levels). Using the spreadsheet for the procedures described by the FAO Manual for establishing tolerance levels when using monitoring data (see 3rd Edition; FAO Plant Production and Protection Paper 225, Third Edition, ISSN 0259-2517; Section 5.11, page 103), the recommended tolerance level for residues of difenoconazole in/on pepper, black would be 0.1 ppm. ChemSAC is in agreement with the recommended tolerance (see ChemSAC meeting

minutes from 8/26/2020). HED notes that as indicated by the FAO Manual, it is not unexpected that when large numbers of residue data are input into the spreadsheet, the highest residues may be above the recommended tolerance level determined by this process.

For Japanese persimmon (Petition Number 9E8793; D454717, Morton, T., 9/14/2020). Syngenta is petitioning for a tolerance with no U.S. registration for residues of difenoconazole in/on Japanese persimmon imported from Japan at 0.7 ppm. Syngenta has submitted a summary of Japanese persimmon field trial data reflecting the maximum use rate in Japan in support of this petition which was previously submitted to Japan. Using the OECD tolerance calculation procedures, the tolerance in/on persimmon, Japanese is 0.5 ppm; however, HED is recommending for a tolerance of 0.7 ppm to harmonize with Japan's MRL in/on Japanese persimmon of 0.7 ppm.

5.3 Water Residue Profile

The drinking water estimates used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED; D435066, Khan, F., 5/02/2017). EFED will not conduct a new drinking water assessment for difenoconazole for registration review (confirmation email from Khan, F. to Page, J. dated 5/07/2019 and confirmation email from Orrick, G. to Morton, T. dated 4/07/2020). For surface water, the recommended EDWCs for human health are **33.4** µg/L (ppb) for the acute dietary (food plus water) exposure analysis and **27.4** µg/L (ppb) for the chronic dietary (food plus water) exposure analysis (1-in-10 year annual mean).

Table 5.3.1. Maximum EDWCs for Difenoconazole Residues of Concern

Source	Peak Exposure (µg/L)	Annual Mean Exposure (µg/L)	30-year Average Exposure (µg/L)
Surface water	33.4[A]	27.4[A]	9.9[B]
Groundwater[C]	2.0	0.60	0.60

[A] EDWCs generated using Tier 1 Rice model for aerial application of 0.244 lbs a.i./A/Y for rice/wild rice use and the release of irrigation or flooded paddy water for 7 days after the last application.
[B] EDWCs generated using the Surface Water Concentration Calculator (SWCC) model for aerial application of 0.46 lbs a.i./A/Y for grape use.
[C] Groundwater EDWCs are based on the PWC (PRZM-GW module) 100 years simulation for FL citrus scenario and the highest difenoconazole application rate of 0.50 lb a.i./A/Y for citrus.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

The acute analysis assumed tolerance-level residues and 100 PCT for all the registered and proposed crops. Tolerance-level residues were also assumed for all livestock commodities in this assessment. The chronic analysis assumed tolerance-level residues and average PCT information for some commodities. Empirical processing factors were used for apple/pear juice (0.04x), dried plums (2.6x), citrus juices (0.1x), grape juice (0.2x), potato chips (0.5x), potato granules/flakes/flour (0.5x), sugar beet molasses (0.6x), tomato paste (1.6x), and tomato puree

(0.5x); and HED's 2018 Default Processing Factors were assumed for other processed commodities.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute dietary exposure analyses assumed 100 PCT. Average PCT (see Screening Level Analysis (SLUA) report dated 3-June-2019 prepared by BEAD) was used in the chronic dietary exposure analysis for the following crops: almond 15%, apples 20%, apricot 10%, artichoke 15%, blueberry 10%, broccoli 2.5%, cabbage 10%, cantaloupe 2.5%, carrot 2.5%, cauliflower 2.5%, cherry 2.5%, cucumbers 5%, garlic 5%, grapefruit 10%, grape 25%, hazelnut 2.5%, lemon 5%, onions 5%, orange 5%, peach 5%, pear 10%, pecan 5%, peppers 10%, pistachio 5%, plum/prune 5%, potato 15%, pumpkin 5%, soybean 2.5%, squash 5%, strawberry 2.5%, sugar beets 20%, tangerine 5%, tomato 35%, walnut 5%, watermelon 10%, and wheat 10%. For other commodities 100 PCT was used.

5.4.3 Acute Dietary Risk Assessment

The unrefined acute analysis assumed tolerance-level residues, 100 PCT, and the available empirical or HED's 2018 Default Processing Factors. The peak estimated drinking water concentration (EDWC) of 33.4 µg/L (ppb) was used for the acute dietary exposure analysis. The resulting acute food plus water dietary exposure estimates were less than HED's level of concern (i.e., <100% of the acute population-adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the general U.S. population (17% aPAD) and all population subgroups. The most highly exposed population subgroup was all infants <1 year old at 53% aPAD.

5.4.4 Chronic Dietary Risk Assessment

The partially refined chronic analysis assumed tolerance-level residues, the available empirical or HED's 2018 Default Processing Factors, and average PCT information for some commodities. The 1-in-10 year annual mean EDWC of 27.4µg/L (ppb) was used for the chronic dietary exposure analysis. The resulting chronic food plus water dietary exposure estimates were less than HED's level of concern (i.e., <100% of the chronic population-adjusted dose (cPAD)) for the general U.S. population (11% cPAD) and all population subgroups. The most highly exposed population subgroup was all infants <1 year old at 38% cPAD.

5.4.5 Cancer Dietary Risk Assessment

Based on the available data, it was determined that the RfD approach used for chronic dietary exposure assessment is adequately protective of all chronic toxicity, including carcinogenicity, that could result from exposure to difenoconazole. Therefore, a separate cancer dietary risk assessment was not required.

5.4.6 Summary Table

Table 5.4.6.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Difenoconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.042454	17	0.005669	11	Not Applicable	Not Applicable
All Infants (<1 year old)	**0.131967**	**53**	**0.019020**	**38**		
Children 1-2 years old	0.112936	45	0.015073	30		
Children 3-5 years old	0.081133	32	0.010692	21		
Children 6-12 years old	0.052841	21	0.006497	13		
Youth 13-19 years old	0.027448	11	0.003828	7.7		
Adults 20-49 years old	0.030995	12	0.005000	10		
Adults 50+ years old	0.030498	12	0.004748	9.5		
Females 13-49 years old	0.030326	12	0.004351	8.7		

**The values for the highest exposed population is bolded.*

5.4.7 Summary Findings of Separate Dietary Assessment for Triazole Metabolites

The unrefined dietary exposure analyses for the triazole metabolites were updated for registration review for difenoconazole, pending tolerances with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793), olive (Petition No. 9E8814), and pepper, black (Petition No. 0E8834), new uses of mefentrifluconazole, and revised EDWCs for triazole metabolites (D458686/D458687, Morton, T., 9/14/2020). The results from the most recent triazole dietary analyses are below HED's level of concern. See Table 5.4.7.1.

Table 5.4.7.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites Adding the New Uses for Difenoconazole and Mefentrifluconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
1,2,4-Triazole						
General U.S. Population	0.008154	27	0.001772	35	Not Applicable	Not Applicable
All Infants (< 1 year old)	0.013186	44	0.003524	71		
Children 1-2 years old	**0.020003**	**67**	**0.004316**	**86**		
Children 3-5 years old	0.017658	59	0.003371	67		
Children 6-12 years old	0.010171	34	0.001988	40		
Youth 13-19 years old	0.006729	22	0.001345	27		
Adults 20-49 years old	0.006728	22	0.001595	32		
Adults 50-99 years old	0.006006	20	0.001553	31		
Females 13-49 years old	0.006763	23	0.001576	32		
Triazolylalanine + Triazolylacetic Acid						
General U.S. Population	Not Applicable	Not Applicable	0.012978	14	Not Applicable	Not Applicable
All Infants (< 1 year old)			0.019476	22		
Children 1-2 years old			**0.040440**	**45**		
Children 3-5 years old			0.031920	36		

Table 5.4.7.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites Adding the New Uses for Difenoconazole and Mefentrifluconazole.						
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
Children 6-12 years old			0.017425	19		
Youth 13-19 years old			0.010621	12		
Adults 20-49 years old			0.010673	12		
Adults 50-99 years old			0.010129	11		
Females 13-49 years old	**0.069639**	**70**	0.010365	12		

* The values for the highest exposed population for each type of risk assessment are bolded.

6.0 Residential Exposure/Risk Characterization

There are no proposed residential uses at this time; however, there are existing residential uses that were previously reassessed (D457340, Mottley, C., 9/14/2020) to reflect updates to HED's 2012 Residential SOPs[3] along with policy changes for body weight assumptions. The proposed new tolerances with no U.S. registrations will not impact the recommendations for the residential exposures for the difenoconazole aggregate assessment.

6.1 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.1.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for difenoconazole. These recommendations remain unchanged from the recent comprehensive human health risk assessment for registration review (D457325, Cropp-Kohlligian, B. *et al*., 9/18/2020).

- The recommended residential exposure for use in the adult aggregate assessment is handler inhalation exposures from applications to gardens/ornamentals via hose-end sprayer.

Table 6.1.1. Recommendations for the Residential Exposures for the Difenoconazole Aggregate Assessment.			
Formulation	Application Equipment/Method	Inhalation Absorbed Dose (mg/kg/day)[1]	Inhalation MOE[2] (LOC = 100)
Gardens/Ornamentals			
Ready-to-use	Hose-end Sprayer	0.0000078	3,200,000

1 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or sq ft) × Area Treated (A/day or sq ft/day) ÷ BW (69 kg).
2 Inhalation MOE = Inhalation POD (25 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

7.0 Aggregate Exposure/Risk Characterization

In accordance with the Food Quality Protection Act (FQPA), HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks

[3] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

Current agency policy is to combine exposure from food and drinking water only for acute aggregate risk assessment. Acute aggregate risk, therefore, is equivalent to the acute dietary risk (Section 5.4.3). No acute dietary risks of concern were identified for exposure to difenoconazole. Hence, there are no acute aggregate risks of concern.

7.2 Short-Term Aggregate Risk

Short-term aggregate assessments are expected when there are residential uses. Short-term aggregate risk was estimated by combining chronic dietary exposure (food + water) with the residential handler inhalation exposures from applications to gardens/ornamentals via hose-end sprayer. There is no risk of concern from short-term aggregate exposure; the resulting risk estimate is an MOE of 5,000 (LOC = 100).

Table 7.2.1. Short-Term Aggregate Risk Calculations.

Population	Short-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adults	25	100	0.25	0.005000	0.0000078	0.005008	5,000

[1] From 10x interspecies extrapolation factor (UFA) and 10x intraspecies variability factor (UFH), along with a FQPA SF of 1x.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. See Table 6.1.1.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure).
[5] Aggregate MOE = [NOAEL/(Avg Food & Water Exposure + Residential Exposure)].

7.3 Intermediate-Term Aggregate Risk

Intermediate-term aggregate assessments include exposures that will occur from thirty days to six months. Intermediate-term exposures for residential handlers are not likely because of the intermittent nature of applications by homeowners. A quantitative exposure/risk assessment for residential post application exposures was not performed. Hence, a quantitative intermediate-term aggregate risk assessment was not required.

7.4 Chronic Aggregate Risk

Chronic aggregate assessments include exposures that are expected to exceed six months. There are no long-term residential exposures for difenoconazole. Therefore, similar to acute aggregate assessment, only chronic dietary exposures (food + water) were evaluated, and chronic aggregate assessment is equivalent to chronic dietary risk (Section 5.4.4). No chronic dietary risks of concern were identified for difenoconazole. Hence, there are no chronic aggregate risks of concern.

7.5 Cancer Aggregate Risk

Based on the available data, it was determined that the RfD approach used for chronic dietary exposure assessment is adequately protective of all chronic toxicity, including carcinogenicity, that could result from exposure to difenoconazole. Therefore, a separate cancer aggregate assessment was not required.

7.6 Summary Findings of Separate Aggregate Assessment for Triazole Metabolites

Application of difenoconazole also results in potential exposures to the triazole metabolites: 1,2,4-triazole, triazolylalanine, and triazolylacetic acid. These compounds are considered to be toxicologically different from difenoconazole. HED recently conducted a separate aggregate risk assessment for these compounds with the resulting exposure estimates less than HED's level of concern (D458929, Morton. T., 9/14/2020).

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for difenoconazole. The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information). [4] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).

[4] Available: http://www.epa.gov/reducing-pesticide-drift

During registration review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for difenoconazole.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to difenoconazole and any other substances[5]. Although the conazole fungicides (triazoles) produce 1,2,4 triazole and its acid-conjugated metabolites (triazolylalanine and triazolylacetic acid), 1,2,4 triazole and its acid-conjugated metabolites do not contribute to the toxicity of the parent conazole fungicides (triazoles). The agency has assessed the aggregate risks from the 1,2,4 triazole and its acid-conjugated metabolites (triazolylalanine and triazolylacetic acid) separately. Difenoconazole does not appear to produce any other toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that difenoconazole has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[6] and conducting cumulative risk assessments (CRA)[7]. During registration review, the agency will utilize this framework to determine if the available toxicological data for difenoconazole suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

Since the proposed uses of difenoconazole are all non-domestic, there is no potential for domestic occupational exposures. An occupational exposure and risk assessment is not required.

12.0 References

Chen, J. December 18, 2008. TXR 0056473. Difenoconazole - with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

[5] EPA's assessments of conazoles prior to the development of the 2016 Framework document noted the lack of conclusive data to make a common mechanism of toxicity finding for the conazoles.

[6] Guidance *for* Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)

[7] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

Cropp-Kohlligian, B. *et al*. September 18, 2020. D457325. Difenoconazole. Draft Human Health Risk Assessment for Registration Review.

Cropp-Kohlligian, B. March 23. 2021. D457342. Difenoconazole. Tolerance with No U.S. Registration for Imported Olives. Summary of Analytical Chemistry and Residue Data.

Cropp-Kohlligian, B. March 23, 2021. D458676. Difenoconazole. Tolerance with No. U.S. Registration for Imported Black Pepper Based on Monitoring Data. Summary of Analytical Chemistry and Residue Data.

Irwin, W. September 19, 2011. D391350. Difenoconazole: Report of the Residues of Concern Knowledgebase Sub-committee (ROCKS).

Khan, F. May 2, 2017. D435066. Difenoconazole: Drinking Water Exposure Assessment in Support of Proposed New Uses on Guava, Papaya, Cranberry and Watercress and expansion of use on Small Fruit Vine Subgroup (13-07F) Except Fuzzy Kiwi Fruits.

Knizner, S. May 27, 2009. No DP Barcode, No TXR Number. HED Interim Guidance on Tolerance Expressions.

Morton, T. September 14, 2020. D457341 & D458677. Difenoconazole. Acute and Chronic Aggregate Dietary (Food + Water) Exposure and Risk Assessments for the Establishment of a Tolerance with No U.S. Registration in/on Imported Olive and Black Pepper in addition to the Registration Review of Difenoconazole. Note: While the document title does not specify it, this assessment also included the pending tolerance with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793).

Morton, T. September 14, 2020. D458686 & D458687. Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address the Establishment of a Difenoconazole Tolerances with No U.S. Registration for Imported Olive and Black Pepper and to include updated Estimated Drinking Water Concentrations. Note: While the document title does not specify it, this assessment also included the pending tolerance with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793).

Morton, T. September 14, 2020. D458929. Common Triazole Metabolites: Updated Aggregate Human Health Risk Assessment to Address the Establishment of a Difenoconazole Tolerances with No U.S. Registration for Imported Olive and Black Pepper and to include updated Estimated Drinking Water Concentrations. Note: While the document title does not specify it, this assessment also included the pending tolerance with no U.S. registrations for residues of difenoconazole in/on imported Japanese persimmon (Petition No. 9E8793).

Morton, T. September 14, 2020. D454717. Difenoconazole. Petition for the Establishment of a Tolerance with No U.S. Registration in/on Imported Japanese Persimmon. Summary of Analytical Chemistry and Residue Data (Petition No. 9E8793).

Mottley, C. September 14, 2020. D457340. Difenoconazole. Occupational and Residential Exposure Assessment in Support of Difenoconazole Registration Review.

Shah, P. March 1, 2007. TXR 0054532, D318039. DIFENOCONAZOLE (PC Code 128847). Request for Restatement of 1994 EPA Cancer Classification and Risk Assessment Approach Using Current Terminology.

Smegal, D. March 5, 2012. TXR 0054074. Difenoconazole: Summary of Hazard and Science Policy Council (HASPOC) Meeting of February 23, 2012: Recommendations on the need for a 28-day inhalation study.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) food uses for difenoconazole are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	--
870.3465	90-Day Inhalation	yes	--[8]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	Yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	Yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	No	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Develop. Neurotoxicity	no	--
870.7485	General Metabolism	Yes	yes
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	yes	yes

[8] Not required at this time, according to the Hazard and Science Policy Council (TXR 0054074, Smegal, D., 03/05/2012).

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Difenoconazole				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral (rat)	42090006	LD_{50} = 1453 mg/kg (M & F)	III
870.1200	Acute dermal (rabbit)	42090007	LD_{50} > 2010 mg/kg (M & F)	III
870.1300	Acute inhalation (rat)	42090008	LC_{50} > 3.3 mg/L (M & F)	III
870.2400	Eye irritation (rabbit)	42090009	Moderately irritating	III
870.2500	Dermal irritation (rabbit)	42090010	Slight irritation	IV
870.2600	Skin sensitization (guinea pig)	42090011 42710004	Negative	N/A

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Difenoconazole		
Guideline No./ Study Type	**MRID (year)/ Classification/Doses**	**Results/ TXR (date)**
870.3100 90-Day oral toxicity (rat)	42090022 (1987) Acceptable/guideline 0, 20, 200, 750, 1500 or 3000 ppm 0, 1.3, 12, 48, 100 or 203 mg/kg/day males 0, 1.6, 62, 124 or 261 mg/kg/day females	NOAEL = 62 mg/kg/day LOAEL = 124 mg/kg/day based on based on decreased body weights (≥10%) in females. TXR 0058051 (2020)
870.3100 90-Day oral toxicity (mouse)	42090021 (1987) Acceptable/guideline 0, 20, 200, 2500, 7500 or 15,000 ppm 0, 3.2, 33, 418, 1590 or 3784 mg/kg/day males 0, 4.4, 43 or 607 mg/kg/day females (top 2 dose groups died before daily intake could be calculated)	NOAEL = 33/43 mg/kg/day (m/f) LOAEL = 418/607 mg/kg/day (m/f) based on increased liver weight, increased incidence and severity of diffuse hepatocellular enlargement and hepatic vacuolation in both sexes, and hepatic coagulative necrosis in females. TXR 0058051 (2020)
870.3200 21/28-Day dermal toxicity (rabbit)	42090013 (1987) Acceptable/guideline 0, 10, 100 and 1000 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on 16% decreased body weight, elevated serum levels of bilirubin and increased incidence of hepatocyte vacuolation in females only. TXR 0058051 (2020)
870.3200 21/28-Day dermal toxicity (rat)	46950310 (2000) Acceptable/guideline 0, 10, 100 and 1000 mg/kg/day	**Systemic** NOAEL = 1000 mg/kg/day LOAEL was not determined. **Dermal** NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on hyperkeratosis at the skin application site. TXR 005446 (2007)

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Difenoconazole		
Guideline No./ Study Type	**MRID (year)/ Classification/Doses**	**Results/ TXR (date)**
870.3700a Prenatal developmental (rat)	42090016, 42710007 (1987) Acceptable/guideline 0, 1.4, 16, 85 or 171 mg/kg/day	**Maternal** NOAEL = 171 mg/kg/day LOAEL was not detected. **Developmental** NOAEL = 171 mg/kg/day LOAEL was not detected. TXR 0058051 (2020)
870.3700b Prenatal developmental (rabbit)	42090017, 42710008 (1987) Acceptable/guideline 0, 1, 25 or 75 mg/kg/day	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on abortions (2/15 pregnant) on gestation days 18 and 24. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on abortions (2/15 pregnant) on gestation days 18 and 24. TXR 0058051 (2020)
870.3800 Reproduction and fertility effects (rat)	42090018 (1988) Acceptable/guideline 0, 25, 250 or 2500 ppm 0, 1.7, 18 or 172 mg/kg/day P males 0, 2.0, 20 or 192 mg/kg/day P females 0, 1.4, 14 or 147 mg/kg/day F_1 males 0, 1.6, 16 or 169 mg/kg/day F_1 females	**Parental** NOAEL = 20 mg/kg/day LOAEL = 192 mg/kg/day based on decreased body weight (≥ 10%) in P and F1 females, and in F1 males. **Reproductive** NOAEL = 192 mg/kg/day LOAEL was not determined. **Offspring** NOAEL = 20 mg/kg/day LOAEL = 192 mg/kg/day based on decreased mean pup body weight that progressed over time (6-8% at birth to 29-33% at weaning). TXR 0058051 (2020)
870.4100b Chronic toxicity 28 weeks (dog)	42090012 (1988) Acceptable/guideline 0, 100, 1000, 3000 or 6000 ppm 0, 3.6, 31, 97 or 158 mg/kg/day males 0, 3.4, 35, 111 or 204 mg/kg/day females	NOAEL = 31 mg/kg/day LOAEL = 97 mg/kg/day based on incidence of cataracts in both sexes. TXR 0058051 (2020)
870.4100b Chronic toxicity 52 weeks (dog)	42090014, 42710005 (1988) Acceptable/guideline 0, 20, 100, 500 or 1500 ppm 0, 0.71, 3.4, 16 or 51 mg/kg/day males 0, 0.63, 3.7, 19 or 44 mg/kg/day females	NOAEL = 51 mg/kg/day LOAEL was not determined. TXR 0058051 (2020)

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Difenoconazole		
Guideline No./ Study Type	**MRID (year)/ Classification/Doses**	**Results/ TXR (date)**
870.4300 Combined Chronic Toxicity/Carcinogenicity (rat)	42090019, 42710010 (1989) Acceptable/guideline 0, 10, 20, 500 or 2500 ppm M: 0, 0.48, 0.96, 24 and 124 mg/kg/d F: 0, 0.64, 1.3, 33 and 170 mg/kg/day	NOAEL = 24 mg/kg/day LOAEL = 124 mg/kg/day based on decreased (22-23%) body weight in females, as well as decreased (18-24%) platelet counts and increased (14-48%) albumin/globulin ratio in males. No evidence of carcinogenicity. TXR 0058051 (2020)
870.4300 Combined Chronic Toxicity/Carcinogenicity (mouse)	42090015, 42710006 (1989) Acceptable/guideline 0, 10, 30, 300, 2500 or 4500 ppm 0, 1.5, 4.7, 46, 423 or 819 mg/kg/day males 0, 1.9, 5.6, 58 or 513 mg/kg/day females (highest ppm dose female group died by week 2)	NOAEL = 4.7 mg/kg/day LOAEL = 46 mg/kg/day based on increased incidence of liver lesions (individual cell necrosis and bile stasis in males, hepatocyte hypertrophy in both sexes), and increased serum levels of SDH in males. Increased incidence of hepatocellular adenoma was seen in females at 56 mg/kg/day, and in males at 819 mg/kg/day. Increased incidence of hepatocellular carcinoma was seen in males at 46 mg/kg/day and higher dose. TXR 0058051 (2020)
870.5100 Bacterial reverse mutation test (*S. typhimurium* and *E. coli*)	42090025 (1990) Acceptable/guideline 85 - 1362 µg/plate +/- S9	Not cytotoxic nor mutagenic at soluble doses (≤ 340µg/plate) in *S. typhimurium* strains TA1535, TA1537, TA98 or TAl00, or in *E. coli* strain WP2uvra. TXR 0009689 (1992)
870.5300 *In vitro* mammalian cell gene mutation test (mouse lymphoma cell, L5178Y/TK+/-)	42090024 (1986) Unacceptable	No conclusions can be reached from the forward mutation assays. TXR 0009689 (1992)
870.5375 *In vitro* mammalian chromosomal aberrations test (Chinese hamster ovary cells)	46950319 (2001) Acceptable/guideline 0, 21.99, 27.49, or 34.36 µg/mL (-S9) 0, 34.36, 53.69 or 67.11 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix. TXR 0054460 (2007)
870.5375 *In vitro* mammalian chromosomal aberrations test (Chinese hamster ovary cells)	46950321 (2001) Acceptable/guideline 0, 26.3, 39.5 or 59.3 µg/mL (-S9) 0, 11.7 or 17.6 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background. TXR 0054460 (2007)
870.5375 *In vitro* mammalian chromosomal aberrations test (human lymphocytes)	46950323 (2001) Acceptable/guideline 0, 5, 30 or 75 µg/mL (-S9) 0, 5, 30 or 62 µg/mL (+S9)	There was no evidence of structural chromosomal aberrations induced over background. TXR 0054460 (2007)

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Difenoconazole		
Guideline No./ Study Type	**MRID (year)/ Classification/Doses**	**Results/ TXR (date)**
870.5385 Mammalian bone marrow chromosomal aberration test (Chinese hamster)	42090023 (1986) Unacceptable 250, 500 or 1000 mg/kg	No unscheduled deaths or other clinical signs of toxicity were reported for any treatment group. There was no evidence of a cytotoxic effect on the target organ or significant increase in the frequency of nuclear anomalies (micronuclei). However, the study was compromised by design and the lack of a MTD. TXR 0009689 (1992)
870.5395 Mammalian erythrocyte micronucleus assay (mice)	42710011 (1992) Acceptable/guideline 0, 400, 800 or 1600 mg/kg	No increase in micronucleated polychromatic erythrocytes occurred. TXR 0010588 (1993)
870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture (primary rat hepatocytes)	42710012 (1992) Acceptable/ guideline 0, 0.46, 1.39, 4.17, 12.5, 25 or 50 µg/mL	Negative as measured by an autoradiographic method. TXR 0010588 (1993)
870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture (primary rat hepatocytes)	42090027 (1985) Unacceptable 0, 0.25, 1.25, 6.25 or 31.25 µg/mL	No conclusion can be reached. The sensitivity of the study was severely compromised. TXR 0009689 (1992)
870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture (human fibroblasts)	42090026 (1985) Unacceptable 0, 0.08, 0.4, 2.0 or 10 µg/mL	No conclusions can be reached. While there was no evidence that the test material was genotoxic, there was also no evidence that a cytotoxic concentration was reached. TXR 0009689 (1992)
870.6200a Acute neurotoxicity screening battery	46950327 (2006) Acceptable/guideline 0, 25, 200 or 2000 mg/kg/day	NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day based on decreased fore-limb strength at the time of peak effect in males. TXR 0058051 (2020)
870.6200b Subchronic neurotoxicity screening battery	46950329 (2006) Acceptable/guideline 0, 40, 250, or 1500 ppm 0, 2.8, 17 or 107 mg/kg/day males 0, 3.2, 20, or 120 mg/kg/day females	NOAEL = 120 mg/kg/day LOAEL was not detected TXR 0058051 (2020)

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Difenoconazole		
Guideline No./ Study Type	**MRID (year)/ Classification/Doses**	**Results/ TXR (date)**
870.7485 Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) Supplementary Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	CGA-169374 was rapidly and extensively distributed, metabolized, and excreted for all dosing regimens. The extent of absorption is undetermined pending determination of the extent of biliary excretion. Recovery after 4 days was 98-108% of the administered dose (AD) for all doses. Elimination in feces (78-95% AD) and urine (8-22% AD) were comparable for all doses, slightly higher in feces of the high dose than the low dose. Blood levels peaked at 24-48 hours for all doses. Elimination half-lives: 20 hours low dose, 33-48 hours high dose. All tissues contained <1% AD 7 days post exposure. Metabolites accounted for most of the recovery. Three major metabolites (A, B, and C) were identified in the feces. Metabolite C was detected only at high dose, indicating that metabolism is dose-related and involve saturation of the metabolic pathway. Free triazole metabolite was detected in urine and its byproduct was detected in the liver. Other urinary metabolites were not characterized. Distribution, metabolism, and elimination was similar for both sexes and for CGA-169374 labeled at the phenyl or triazole rings. TXR 0010588 (1993)
870.7600 *In vivo* Dermal Penetration in rat	Study 1: 47453201 (2007) 10, 100, or 1000 µg/cm^2 Study 2: 46950333 (2003) 0.5, 13 or 2.5 µg/cm^2	Study 1: Most of the dose (80-92%) remained on the skin surface and was removed with mild washing. Absorption, though minimal, generally increased over time. Mean combined absorption at 10, 24, and 72 hours were: 11.3%, 13.8%, and 13.0% from 10 µg/cm^2 dose; 4.1%, 4.3%, and 5.3% from 100 µg/cm^2 dose; and 1.4%, 2.4%, and 2.8% from 1000 ug/cm^2 dose. A dermal absorption factor of 13.8% (10 µg/cm^2 dose, 24 hours after exposure) is appropriate. Study 2: After 6-hour exposure, 27%, 13%, and 9% of the dose was absorbed for the low, mid-, and high-dose, respectively. At 24 hours, 48%, 19% and 8% of the dose was absorbed. The majority of the absorbed dose was isolated in the gastrointestinal tract or carcass at 6 and 24 hours, with increasing amounts found in the feces at 48 and 72 hours. Blood levels during and after exposure were mostly at or below the limit of detection. The highest blood levels were reached between 6 and 8 hours after exposure, accounting for 0.01 ppm and 0.25 ppm. Most of the dose was washed off. A dermal absorption factor of 48% (0.5 µg/cm^2, 24 hours after exposure) is appropriate. In conclusion, a dermal absorption factor of 48% is appropriate based solely on the *in vivo* dermal absorption studies. TXR 0056473 (2008)

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Difenoconazole		
Guideline No./ Study Type	**MRID (year)/ Classification/Doses**	**Results/ TXR (date)**
870.7600 *In vitro* Absorption through Rat or Human Epidermis;	Study 1 (rat): 47453202 (2007) 10, 100, or 1000 µg/cm2 Study 2 (human): 47453203 (2007) 10, 100, or 1000 µg/cm2	Study 1 (rat): For the 10-hour exposure period, the percent dermal absorbed are 26%, 2.8% and 2.9% of the applied dose of 10, 100, or 1000 µg/cm^2, respectively. For the 24-hour exposure period, the percent dermal absorbed are 40%, 17% and 3.3 % of the applied dose of 10, 100, or 1000 µg/cm^2, respectively. Study 2 (human): At 10 hours, absorption was 3.46%, 1.15% and 0.44% for 10, 100, and 1000 µg/cm^2, respectively. At 24 hours, the absorption was 4.54%, 1.30% and 0.40% for the 10, 100, and 1000 µg/cm^2, respectively. Conclusion: The 24-hour exposure period is more appropriate in comparing the difference between *in vitro* rat vs. human skin studies. The data set with the highest ratio should be used as the adjustment factor. Therefore, the dataset derived from 1000 µg/cm^2 which gave the highest ratio of 0.12 should be used for the derivation of the estimated human dermal absorption factor. TXR 0056473 (2008)
870.7800 Immunotoxicity (mouse)	48696701 (2011) Acceptable/guideline 0, 20, 200, 1000, or 1500 pm 0, 3, 35, 177 or 247 mg/kg/day	**Systemic NOAEL** = 35 mg/kg/day **Systemic LOAEL** = 177 mg/kg/day based on decreased body weight gains and liver toxicity **Immunotoxicity NOAEL** = 35 mg/kg/day **Immunotoxicity LOAEL** = 177 mg/kg/day based on decreased mean anti-SRBC IgM levels. TXR 0056379 (2012) This review is conservative; however, it will not be updated at this time because an update would not impact the risk assessment.

A.3 Literature Search for Difenoconazole

Date and Time of Search: 03/27/2020; 07:23 am

Search Details: ((*Difenoconazole*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

Studies Identified in PubMed*: 23

SWIFT-Review** Tags:
8 for Animal
18 for Human
0 for NO TAG

All studies identified in the PubMed search were screened when the citation list was ≤100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag.

Number of Articles Identified as Relevant for Risk Assessment: 1

Citations of Articles Identified as Relevant for Risk Assessment:

Ribas Pereira, Viviane *et al.* "Sperm quality of rats exposed to difenoconazole using classical parameters and surface-enhanced Raman scattering: classification performance by machine learning methods" *Environmental Science and Pollution Research* 26. (2019): 35253–35265.

Conclusion of Literature Search: Following a full text review, no studies were identified that contained relevant information (either quantitative or qualitative) that would impact the risk assessment or that would be considered in the selection of Points of Departure (PODs) for the difenoconazole human health registration review risk assessment.

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.

**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize citations lists that were larger than 100. Studies identified in the PubMed search were tagged and grouped based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Difenoconazole.

Parameter	Value	Reference
Melting point	78.6 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
pH	6-8 at 20 °C (saturated solution)	
Density	1.37 g/cm^3 at 20 °C	
Water solubility	3.3 ppm at 20 °C	
Solvent solubility	g/100 mL at 25 °C: n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10^{-10} mm Hg at 25 °C	
Dissociation constant, pK_a	pure grade (99.3% ± 0.3%) difenoconazole in water (with 4% methanol) at 20°C is 1.1	DP# 375159, 5/26/10, B. Cropp-Kohlligian
Octanol/water partition coefficient, Log(K_{OW})	4.2 at 25 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
UV/visible absorption spectrum	λ_{max} at about 200 and 238 nm (in methanol at 26 °C)	PMRA Proposed Regulatory Decision Document on Difenoconazole, 4/14/99 (PRDD99-01)

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Outdoor Residential Exposure Task Force (ORETF) database and are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the agency website[9].

[9] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix D. International Residue Limit Status Sheet.

Table D.1. Summary of US and International Tolerances and Maximum Residue Limits.

Residue Definition:

U.S. - 40 CFR §180.475(a)(1): Plant: Difenoconazole

Canada - Plant: Difenoconazole

Codex - Plant: Difenoconazole

Commodity	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S.[1]	Canada	Mexico[2]	Codex
Olive[3]	3			
Olive, with pit[4]	2	2.5 Olives[5]		2 Table Olives[6]
Pepper, black[7]	0.1			
Persimmon, Japanese	0.7	0.1		4Po[8]

Completed using Global MRL. 7/22/2020

Note 1. The recommended U.S. tolerances which are listed below are without U.S. registrations.

Note 2. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes.

Note 3. "Olive" is defined in OCSPP Guideline 860.1000 as being the fruits after removal of the stems and pits. For residue analysis, OECD and Codex also define olive as the fruits after removal of the stems and pits; however, those organizations stipulate that residues should be expressed on a whole-fruit basis.

Note 4. ChemSAC meeting dates 4/10/2019 and 4/24/2019: ChemSAC recommended adding a commodity term of "Olive, with pit" for tolerance listings for the purposes of harmonization.

Note 5. Canadian MRL is based on the same olive data used for the recommended U.S. tolerance; however, it appears that they used the olive with pit residues and NAFTA tolerance calculation procedures.

Note 6. Codex MRL is based on the same olive data used for the recommended U.S. tolerance and OECD tolerance calculation procedures. Codex defines olive as the fruits after removal of the stems and pits; however, Codex stipulates that residues should be expressed on a whole-fruit basis.

Olive with Pit Data Reviewed by Joint FAO/WHO Meeting on Pesticide Residues (JMPR). In Spain, difenoconazole may be applied to olive trees three times at a spray concentration of 0.015 kg ai/hL with a 30 days PHI. In seven trials in Spain in 2003 – 2005 matching GAP, difenoconazole residue levels were 0.22, 0.29, 0.40, 0.42, 0.51, 0.90 and 1.2 mg/kg. In an olive trial in France with application conditions matching Spanish GAP, difenoconazole residues on olives were 0.76 mg/kg. In summary, difenoconazole residues in olives from eight trials in ranked order (median underlined) were: 0.22, 0.29, 0.40, <u>0.42</u>, <u>0.51</u>, 0.76, 0.90 and 1.2 mg/kg. The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in olives of 2, 0.465 and 1.2 mg/kg respectively.

Note 7. An MRL of 0.6 ppm has been established by Japan on "Other spices." Global MRL notes that this MRL may be relevant to "Pepper (spice)" and this should be confirmed with official sources as Japan does not clearly define "Other spices."

An MRL of 0.3 ppm has been established by the European Union (EU) and the European Economic Area (EEA) on the group "Fruit Spices" which includes: allspice/pimento; Sichuan pepper; Caraway; Cardamom; Juniper berry; Peppercorn (black, green, white); vanilla; Tamarind; Others. The basis of the establishment of this MRL for the crop group "Fruit Spices" is not known.

An MRL of 0.3 ppm has been established by Singapore, Switzerland, and Turkey on "Pepper, black; white."

An MRL of 0.05 ppm has been established by Taiwan on "Others (tea, spices and dried herbs)."

Global MRL does not indicate a MRL for Vietnam.

The Canadian default MRL is 0.1 ppm.

Note 8. Codex includes Japanese persimmon in their pome fruit crop group. Po = Postharvest treatment.